PCT/JP00/06874

23.10.00

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I, LEANNE MYNOTT, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PQ3249 for a patent by FUJISAWA PHARMACEUTICAL CO. and LTD. filed on 04 October 1999.

WITNESS my hand this
Fourth day of October 2000

LEANNE MYNOTT
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Fujisawa Pharmaceutical Co., Ltd.

AUSTRALIA
Patents Act 1990

PROVISIONAL SPECIFICATION
for the invention entitled:

"New Use"

The invention is described in the following statement:

DESCRIPTION

NEW USE

Technical Field

This invention relates to a new use of a plasminogen activator, which is useful in a medical field.

Background art

Various plasminogen activators are well known. And, a certain macrolide compound, i.e., tacrolimus, and its related compounds are known to have preventing or treating activity of cerebral infarction (USP 5,648,351).

Disclosure of Invention

This invention relates to a new use of plasminogen activators, for increasing an effect caused by interleukin 2 inhibitor (hereinafter, referred to IL-2 inhibitor).

Therefore, one object of the present invention is to provide a new use of a plasminogen activator for increasing an effect caused by IL-2 inhibitor.

Another object of this invention is to provide a method for increasing an effect caused by IL-2 inhibitor by administering an effective amount of a plasminogen activator.

A further object of this invention is to provide a use of a plasminogen activator for manufacturing a medicament for increasing an effect caused by IL-2 inhibitor.

Still further object of this invention is to provide a composition comprising a plasminogen activator, for increasing an effect caused by IL-2 inhibitor.

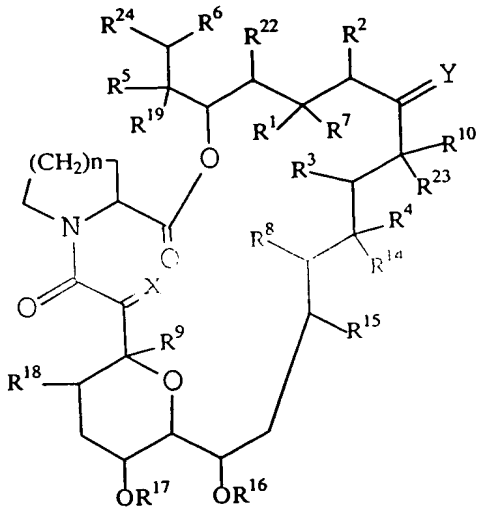
In the present invention, the "plasminogen activator" should not be limited and be considered to mean any compounds which can convert inactivate plasminogen to the protease plasmin. For example, tissue-type plasminogen activator(tPA), urokinase (UK), pro-urokinase, streptokinase, acylated streptokinase/tPA conjugates, etc.

The "IL-2 inhibitor" used in the present invention should not be limited and be considered to mean any ones possessing IL-2 inhibitory activity. The particular example is the one possessing an inhibitory activity on the production of IL-2. And the other is the one that inhibits the transmission of IL-2 signal.

The preferable "effect caused by IL-2 inhibitor" is a neuroptotective activity. Particularly, "the effect caused by IL-2 inhibitor" may be the treatment and prevention of acute or chronic cerebral neurodegenerative diseases, such as cerebral ischemic diseases and/or brain damage caused by ischemia.

Preferable "IL-2 inhibitor" is, for example, the tricyclic macrolide shown in EP-0184162, WO89/05303, WO93/05058, WO96/31514, and so on, the disclosure of which is incorporated herein by reference. It is well known that those tricyclic macrolides have strong IL-2 inhibitory activity.

As a particular example of the tricyclic macrolides compounds, the tricyclic compound of the following formula (I) can be exemplified.



(1)

(wherein each of adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 independently

(a) is two adjacent hydrogen atoms, but R^2 may also be an alkyl group or

(b) may form another bond formed between the carbon atoms to which they are attached;

R^7 is a hydrogen atom, a hydroxy group, a protected hydroxy group, or an alkoxy group, or an oxo group together with R^1;

R^8 and R^9 are independently a hydrogen atom or a hydroxy group;

R^{10} is a hydrogen atom, an alkyl group, an alkyl group substituted by one or more hydroxy groups, an alkenyl group, an alkenyl group substituted by one or more hydroxy groups, or an alkyl group substituted by an oxo group;

X is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula $-CH_2O-$;

Y is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} are independently a hydrogen atom, an alkyl group, an aryl group or a tosyl group;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} are independently a hydrogen atom or an alkyl group;

R^{24} is an optionally substituted ring system which may contain one or more heteroatoms;

n is an integer of 1 or 2; and

in addition to the above definitions, Y, R^{10} and R^{23}, together with the carbon atoms to which they are attached, may represent a saturated or unsaturated 5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring optionally substituted by one or more groups selected from the group consisting of an alkyl, a hydroxy, an alkoxy, a benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and an alkyl substituted by one or more hydroxy groups.

Preferable R^{24} may be cyclo(C_{5-7})alkyl group, and the following ones can be exemplified.

(a) a 3,4-di-oxo-cyclohexyl group;

(b) a 3-R^{20}-4-R^{21}-cyclohexyl group,

in which R^{20} is hydroxy, an alkoxy group, an oxo group, or a $-OCH_2OCH_2CH_2OCH_3$ group, and

R^{21} is hydroxy, -OCN, an alkoxy group, a heteroaryloxy which may be substituted by suitable substituents, a $-OCH_2OCH_2CH_2OCH_3$ group, a protected hydroxy group, chloro, bromo, iodo, aminooxalyloxy, an azido group, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO-$,

in which R^{25} is optionally protected hydroxy or protected amino, and

R^{26} is hydrogen or methyl, or

R^{20} and R^{21} together form an oxygen atom in an epoxide ring; or

(c) cyclopentyl group substituted by methoxymethyl, optionally protected hydroxymethyl, acyloxymethyl (in which the acyl moiety optionally contains either a dimethylamino group which may be quaternized, or a carboxy group which may be esterified), one or more amino and/or hydroxy groups which may be protected, or aminooxalyloxymethyl. A preferred example is a 2-formyl-cyclopentyl group.

The definitions used in the above general formula (I) and the specific and preferred examples thereof are now explained and set forth in detail.

The term "lower" means, unless otherwise indicated, a group having 1 to 6 carbon atoms.

Preferable examples of the "alkyl groups" and an alkyl moiety of the "alkoxy group" include a straight or branched chain aliphatic hydrocarbon residue, for example, a lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl and hexyl.

Preferable examples of the "alkenyl groups" include a straight or branched chain aliphatic hydrocarbon residue having one double-bond, for example, a lower alkenyl group such as vinyl, propenyl (e.g., allyl group), butenyl, methylpropenyl, pentenyl and hexenyl.

Preferable examples of the "aryl groups" include phenyl, tolyl, xylyl, cumenyl, mesityl and naphthyl.

Preferable protective groups in the "protected hydroxy

groups" and the "protected amino" are 1-(lower alkylthio)-(lower)alkyl group such as a lower alkylthiomethyl group (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), more preferably C_1-C_4 alkylthiomethyl group, most preferably methylthiomethyl group;

trisubstituted silyl group such as a tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl, etc.) or lower alkyl-diarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenyl-silyl, etc.), more preferably tri(C_1-C_4)alkylsilyl group and C_1-C_4 alkyldiphenylsilyl group, most preferably tert-butyldimethylsilyl group and tert-butyldiphenylsilyl group; and an acyl group such as an aliphatic, aromatic acyl group or an aliphatic acyl group substituted by an aromatic group, which are derived from a carboxylic acid, sulfonic acid or carbamic acid.

Examples of the aliphatic acyl groups include a lower alkanoyl group optionally having one or more suitable substituents such as carboxy, e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl, etc.;

a cyclo(lower)alkoxy(lower)alkanoyl group optionally having one or more suitable substituents such as lower alkyl, e.g., cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxypropionyl, menthyloxybutyryl, menthyloxypentanoyl, menthyloxyhexanoyl, etc.; a camphorsulfonyl group; or a lower alkylcarbamoyl group having one or more suitable substituents such as carboxy or

protected carboxy, for example, carboxy(lower)alkylcarbamoyl group (e.g., carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl, etc.), tri-(lower)alkylsilyl(lower)alkoxycarbonyl(lower)alkylcarbamoyl group (e.g., trimethylsilylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropylcarbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyldimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl, etc.) and so on.

Examples of the aromatic acyl groups include an aroyl group optionally having one or more suitable substituents such as nitro, e.g., benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl, etc.; and an arenesulfonyl group optionally having one or more suitable substituents such as halogen, e.g., benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.

Examples of the aliphatic acyl groups substituted by an aromatic group include ar(lower)alkanoyl group optionally having one or more suitable substituents such as lower alkoxy or trihalo(lower)alkyl, e.g., phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.

More preferable acyl groups among the aforesaid acyl groups are C_1-C_4 alkanoyl group optionally having carboxy, cyclo(C_5-C_6)alkoxy(C_1-C_4)alkanoyl group having two (C_1-C_4) alkyls at the cycloalkyl moiety, camphorsulfonyl group, carboxy-

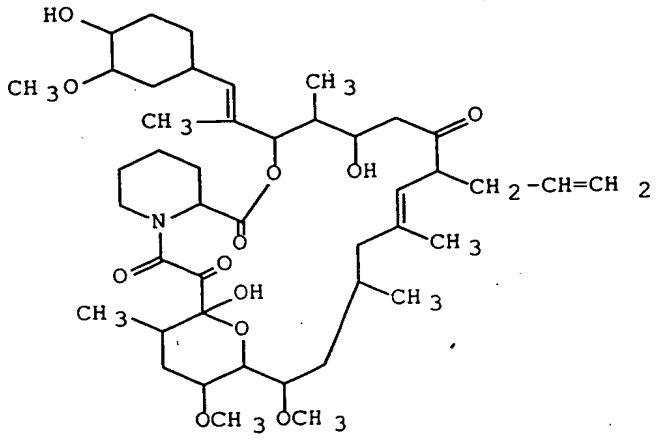
(C_1-C_4)alkylcarbamoyl group, tri(C_1-C_4)alkylsilyl(C_1-C_4)-alkoxycarbonyl(C_1-C_4)alkylcarbamoyl group, benzoyl group optionally having one or two nitro groups, benzenesulfonyl group having halogen, or phenyl(C_1-C_4)alkanoyl group having C_1-C_4 alkoxy and trihalo(C_1-C_4)alkyl group. Among these, the most preferable ones are acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl and 2-trifluoromethyl-2-methoxy-2-phenylacetyl.

Preferable examples of the "5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring" include a pyrrolyl group and a tetrahydrofuryl group.

"A heteroaryl which may be substituted by suitable substituents" moiety of the "heteroaryloxy which may be substituted by suitable substituents" may be the ones exemplified for R^1 of the compound of the formula of EP-A-532,088, with preference given to 1-hydroxyethylindol -5-yl, the disclosure of which is incorporated herein by reference.

The ticyclic compounds (I) and its pharmaceutically acceptable salt for use in accordance with this invention are well known to have excellent immunosuppressive activity, antimicrobial activity and other pharmacological activities and, as such, be of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft-vs-host diseases, autoimmune diseases, and infectious diseases [EP-A-0184162, EP-A-0323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059, etc.].

Particularly, the compounds which are designated as FR900506 (=FK506), FR900520 (ascomycin), FR900523, and FR900525 are products produced by microorganisms of the genus Streptomyces, such as Streptomyces tsukubaensis No. 9993 [deposited with National Institute of Bioscience and Human Technology Agency of Industrial Science and Technology (formerly Fermentation Research Institute Agency of Industrial Science and Technology), at 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan, date of deposit October 5, 1984, accession number FERM BP-927] or Streptomyces hygroscopicus subsp. yakushimaensis No. 7238 [deposited with National Institute of Bioscience and Human Technology Agency of Industrial Science and Technology (formerly Fermentation Research Institute Agency of Industrial Science and Technology), at 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan, date of deposit January 12, 1985, accession number FERM BP-928][EP-A-0184162]. The FK506 (general name: tacrolimus) of the following chemical formula, in particular, is a representative compound.



Chemical name: 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

The preferred examples of the tricyclic compounds (I) are the ones, wherein each of adjacent pairs of R^3 and R^4 or R^5 and R^6 independently form another bond formed between the carbon atoms to which they are attached;

each of R^8 and R^{23} is independently a hydrogen atom;

R^9 is a hydroxy group;

R^{10} is a methyl group, an ethyl group, a propyl group or an allyl group;

X is (a hydrogen atom and a hydrogen atom) or an oxo group;

Y is an oxo group;

each of R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{22} is a methyl group;

R^{24} is a 3-R^{20}-4-R^{21}-cyclohexyl group,

in which R^{20} is hydroxy, an alkoxy group, an oxo group, or a $-OCH_2OCH_2CH_2OCH_3$ group, and

R^{21} is hydroxy, -OCN, an alkoxy group, a heteroaryloxy which may be substituted by suitable substituents, a $-OCH_2OCH_2CH_2OCH_3$ group, a protected hydroxy group, chloro, bromo, iodo, aminooxalyloxy, an azido group, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO-$,

in which R^{25} is optionally protected hydroxy or protected amino, and

R^{26} is hydrogen or methyl, or

R^{20} and R^{21} together form an oxygen atom in an epoxide ring; and

n is an integer of 1 or 2.

The most preferable tricyclic compounds (I) is, in addition to FK506, ascomycin derivatives such as halogenated-ascomycin

(e.g., 33-epi-chloro-33-desoxyascomycin), which is disclosed in EP 427,680, example 66a.

As the other preferable example of the IL-2 inhibitor, rapamycin [THE MERCK INDEX (11th edition), No. 8288] and its derivatives can be exemplified. Preferred example of the derivatives is an O-substituted derivative in which the hydroxy in position 40 of formula A illustrated at page 1 of WO 95/16691, incorporated herein by reference, is replaced by $-OR_1$ in which R_1 is hydroxyalkyl, hydroalkoxyalkyl, acylaminoalkyl and aminoalkyl; for example 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin and 40-O-(2-acetaminoethyl)-rapamycin. These O-substituted derivatives may be produced by reacting rapamycin (or dihydro or deoxo-rapamycin) with an organic radical attached to a leaving group (for example RX where R is the organic radical which is desired as the O-substituent, such as an alkyl, allyl, or benzyl moiety, and X is a leaving group such as $CCl_3C(NH)O$ or CF_3SO_3) under suitable reaction conditions. The conditions may be acidic or neutral conditions, for example in the presence of an acid like trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their respective pyridinium or substituted pyridinium salts when X is $CCl_3C(NH)O$ or in the presence of a base like pyridine, a substituted pyridine, diisopropylethylamine or pentamethylpiperidine when X is CF_3SO_3. The most preferable one is 40-O-(2-hydroxy)ethyl rapamycin, which is disclosed in WO94/09010, the disclosure of which is incorporated herein by reference.

The tricyclic compounds(I), and rapamycin and its

derivatives, may be in a form of its salt, which includes conventional non-toxic and pharmaceutically acceptable salt such as the salt with inorganic or organic bases, specifically, an alkali metal salt such as sodium salt and potassium salt, an alkali earth metal salt such as calcium salt and magnesium salt, an ammonium salt and an amine salt such as triethylamine salt and N-benzyl-N-methylamine salt.

With respect to the IL-2 inhibitor of the present invention, particularly the tricyclic macrolide compounds, it is to be understood that there may be conformers and one or more stereoisomers such as optical and geometrical isomers due to asymmetric carbon atom(s) or double bond(s), and such conformers and isomers are also included within the scope of the present invention. And further, the tricyclic macrolide compounds can be in the form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Further example of the IL-2 inhibitor is cyclosporin and its derivatives such as cyclosporin A, B, C, D, E, F, G, etc, which are shown in THE MERCK INDEX (12th edition), No. 2821, USP 4,117,118, 4,215,199, 4,288,431, 4,388,307, Helv. Chim. Acta. 60, 1568(1977) and 65, 1655(1982), Transplant. Proc. 17, 1362(1985), and so on. Among which, the most preferable one is cyclosporin A. The disclosures of the above references are incorporated herein.

The tricyclic compounds (I) and its pharmaceutically acceptable salts, and cyclosporin or its derivatives may be classified as "IL-2 production inhibitor", which show

immunosuppressive activity by inhibiting the production of IL-2. And rapamycin or its derivatives may be classified as " IL-2 signal transmission inhibitor", which show immunosuppressive activity by inhibiting the transmission of IL-2 signal.

For therapeutic administration, plasminogen activators in the present invention is used in the form of a conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral or external administration. The pharmaceutical preparation may be compounded in a solid form such as granule, capsule, tablet, dragee, suppository or ointment, or in a liquid form such as solution, suspension or emulsion for injection, intravenous drip, ingestion, eye drop, etc. If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent, wetting or emulsifying agent, buffer or any other commonly used additives.

The plasminogen activators as the effective ingredient may usually be administered in an amount which can activate plasminogen to plasmine. In particular, it may be a unit dose of 0.001 mg/kg to 500 mg/kg, preferably 0.01 mg/kg to 10 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, body weight and conditions of the patient or administering method.

For applying this composition to a human, it is preferable to apply it by injection.

In the present invention, a plasminogen activator is able to be administered for increasing the effect caused by a IL-2 inhibitor simultaneously, separately or in sequential use with

a IL-2 inhibitor.

If advisable, the plasminogen activators can be mixed with the IL-2 inhibitor prior to its use. So, the composition comprising the said plasminogen activators of the present invention may further comprise the IL-2 inhibitor. And optionally, it comprises further additional ingredients, such as, mycophenolate moietil (CellCept), steroids, Azathiopurine, and so on.

While the effective dosage of the IL-2 inhibitor depends on the type of the said IL-2 inhibitor, the patient's age, type of disease, severity of illness, and other factors, a daily dose thereof is about 0.01~1000 mg, preferably 0.05~500 mg, and more preferably, 0.1~100 mg for therapeutic purposes. The average unit dose may be generally about 0.1 mg, 0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg, or 500 mg.

When the above-mentioned tricyclic macrolides is used as the IL-2 inhibitor in the present invention, the pharmaceutical composition of the present invention is useful for increasing the effect of the treatment and/or prevention of the following diseases and conditions because of the pharmacologic activities possessed by the said tricyclic macrolides.

The following Preparations and Examples are given for the purpose of illustrating the present invention in detail.

Example 1

Effect of the combination therapy of FK506 and a tissue-type plasminogen activator in a rat middle cerebral artery thrombosis model.

Method)

Animal preparation

Thrombotic occlusion of the MCA was induced by photochemical [illegible] described by Umemura et al., (1993). Briefly, male Sprague-Dawley rats (SLC, Inc.) weighting about 300g were anesthetized with halothane (4% for induction, 1.5% for maintenance). The animals were placed in the lateral position, and the left MCA was exposed by a microsurgical approach. A stable thrombotic occlusion of MCA was produced by photochemical reaction between intravenously administered photoreactive dye, rose bengal (10 mg/kg) and transmural green light(540nm), which causes endothelial injury followed by platelet activation. The body temperature of animals was maintained at 37.0~38.0 °C using a heating-pad. Twenty-four hours after the ischemic insult, the brain was removed for histopathological assessment with triphenyltetrazolium chloride(TTC) staining. The infarct area was calculated by a computerized image analysis system.

Drug treatment

FK506(1 mg/kg) was administered intravenously by a single bolus injection through the femoral vein 2 hours after occlusion of the MCA. A tissue-type plasminogen activator (t-PA)(1 mg/kg) was administered intravenously by a bolus injection (20 % of total volume) followed by infusion (80 % of total volume) for 30 min through the femoral vein 2 hours after occlusion of the MCA. In the combination study, following the administration of FK506, t-PA (1 mg/kg) was administered as described above.

Results)

Therapeutic efficacy of the combination of FK506 and t-PA When drugs were administered 2 hours after occlusion of the MCA, FK506 or t-PA showed a tendency of the inhibition of brain damage. The combination of FK506 and t-PA caused the significant reduction of ischemic brain damage, and its inhibition is more than 23%.

So, the present invention provides useful neuroprotective agent for preventing or treating acute or chronic cerebral neurodegenerative diseases, such as cerebral ischemic diseases and/or brain damage caused by ischemia. So, it is useful when the following diseases or injury occur, that is, cerebral infarction, head injury, hemorrhage in brain such as subarachnoid hemorrhage or intracerebral hemorrhage, cerebral thrombosis, cerebral embolism, cardiac arrest, stroke (such as acute stroke), transient ischemic attacks (TIA), hypertensive encephalopathy, Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) and so on.

From the another aspect, the present invention also provides the following inventions.

i) A use of IL-2 inhibitor for manufacturing a medicament for increasing an effect caused by plasminogen activator, in which the effect caused by plasminogen activator is a neuroprotective activity.

ii) A use of a IL-2 inhibitor and plasminogen activator for manufacturing a medicament for simultaneous, separate or sequential use for neuroprotective activity.

iii) A method for increasing an effect caused by a plasminogen activator, by administering an effective amount of IL-2 inhibitor to a human being or an animal.

iv) A method for preventing and treating acute or chronic cerebral neurodegenerative diseases, by administering an effective amount of a plasminogen activator and an effective amount of IL-2 inhibitor to a human being or an animal.

v) A composition comprising a plasminogen activator and IL-2 inhibitor as a combined preparation for simultaneous, separate or sequential use for neuroprotective activity.

The patents, patent applications and publications cited herein are incorporated by reference.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A use of a plasminogen activator for manufacturing a medicament for increasing an effect caused by IL-2 inhibitor.

2. The use of the claim 1, in which the IL-2 inhibitor inhibits the production of IL-2.

3. The use of the claim 1, in which the IL-2 inhibitor inhibits the activity of IL-2.

4. The use of the claim 1, in which the effect caused by IL-2 inhibitor is a neuroprotective activity.

5. The use of the claim 1, in which the IL-2 inhibitor is tacrolimus or its hydrate, or cyclosporins.

6. A use of a plasminogen activator and IL-2 inhibitor for manufacturing a medicament for simultaneous, separate or sequential use for neuroprotective activity.

7. A method for increasing an effect caused by IL-2 inhibitor, by administering a effective amount of a plasminogen activator to a human being or an animal.

8. A method for preventing and treating acute or chronic cerebral neurodegenerative diseases, by administering a effective amount of a plasminogen activator and an effective amount of IL-2 inhibitor to a human being or an animal.

9. A composition comprising a plasminogen activator, for increasing an effect caused by IL-2 inhibitor.

10. A composition comprising a plasminogen activator and IL-2 inhibitor as a combined preparation for simultaneous, separate or sequential use for neuroprotective activity.

Dated this 4th day of October 1999
Fujisawa Pharmaceutical Co., Ltd.
By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

Abstract

Present invention is relating to a new use of a plasminogen activator, for increasing an effect caused by IL-2 inhibitor.